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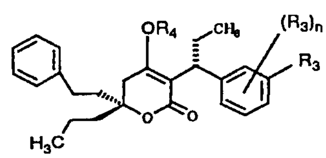
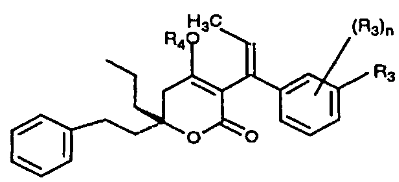


(VIII)



(VII)

(57) Abstract

The present invention is a process for the preparation of a compound of formula (VIII) where R_3, R_4 and n are defined in the specification which comprises hydrogenating a compound of formula (VII) the E–geometrical isomer thereof or a mixture of the Z– and E–isomers in the presence of catalyst containing Rh, a chiral ligand with at least one phosphorous atom where the hydrogenation is conducted in the presence of a base.

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IMPROVED PROCESS FOR ASYMMETRIC HYDROGENATION

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention is an improved process for the asymmetric hydrogenation of a double bond.

2. Description of the Related Art

[R-(R*,R*)]-N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide is a protease inhibitor useful in treating humans infected with the HIV virus (AIDS) and is known as tipranavir.

J. Am. Chem. Soc., 119, 3627 (1997) and the *J. Org. Chem.*, 63, 7348 (1998) both disclose processes to produce tipranavir.

US Patent application Serial No. 09/213,887 discloses a process to convert the ketone (I) to the cyclic ester (VI) as set forth in CHART A and EXAMPLES 1 thru 4 of US Patent application Serial No. 09/213,887. CHART F of US Patent application Serial No. 09/213,887 then discloses the transformation of the cyclic ester (VI) to the corresponding 6(R)- and 6(S)-olefin (XXV) by the process of EXAMPLE 16 which is then hydrogenated by the process of EXAMPLE 17 to produce the nitro-α,β-unsaturated ester (XVII). The nitro-α,β-unsaturated ester (XVII) is then transformed into tipranavir (XIX) by the process of EXAMPLES 14 and 15.

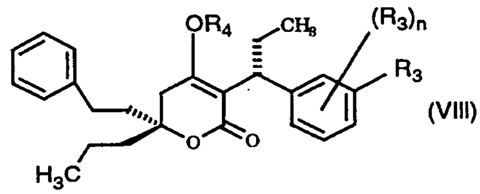
Hydrogenation reactions are very well known to those skilled in the art. In some hydrogenation reactions the product produced has an asymmetric carbon atom as in EXAMPLE 17 of US Patent application Serial No. 09/213,887. It is known to those skilled in the art that the enantioselectivity of the hydrogenation can be influenced by the catalyst used. US Patents 5,171,892, 5,532,395 and 5,559,267 disclose enantioselective rhodium catalysts known as "DuPHOS" catalysts which can provide enantioselective hydrogenations in the 70 to 89% range.

US Patent 5,686,631 and *Tetrahedron Lett.* 37, 8321 (1996) disclose an asymmetric hydrogenation of warfarin, a 2-pyranone derivative, with 89% enantioselectivity with a DuPHOS catalyst. However, warfarin has a phenyl ring attached to the 5,6-position of the compounds of the present invention which would change the three dimensional nature of the compound. *Chem. Rev.* 93, 1307 (1993) and *Chem. Int. Ed. Engl.* 26, 190 (1987) disclose that an important feature in some stereoselective hydrogenation reactions is a secondary coordination of functional groups.

Catalytic Asymmetric Synthesis; VCH, New York, 1993, Chapter 1 and Asymmetric Catalysis in Organic Synthesis, Wiley & Sons, New York , 1993, Chapter 2 disclose an important feature of stereoselective hydrogenation of olefin substrates is the geometry (E or Z) of the double bond. It is known that one isomer of an olefin would be a preferred substrate to obtain higher enantioselectivity of a particular enantiomeric product.

SUMMARY OF INVENTION

Disclosed is a process for the preparation of a compound of the formula:

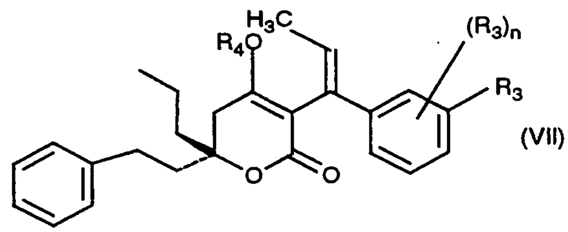


(VIII)

where R_3 is selected from the group consisting of :

- $-NO_2$,
- $-NH_2$,
- $-NH-SO_2-$[4-trifluoromethylpyridin-2-yl],
- $-N(-CH_2-\phi)_2$,
- $-N(R_{3-1})(R_{3-2})$ where R_{3-1} and R_{3-2} are the same or different and are:
  - -H,
  - -CO-O-(*t*-butyl),
  - $-CO-O-CH_2-\phi$,
  - $-CO-CH_3$,
  - $-CO-\phi$,
- -Cl,
- -Br,
- -I,
- -OH,
- $-O-SO_2-CF_3$,

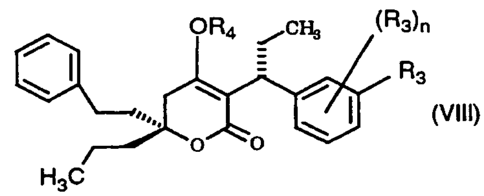
where n is 0 or 1 with the provisos, (1) that when n is 0 the R_3 group must be in the meta position and (2) that when n is 1, one of R_3 must be -Cl, -Br, -I, -OH or $-O-SO_2-CF_3$, where R_4 is selected from the group consisting of -H and $-Si(CH_3)_3$, which comprises hydrogenating a compound of the formula:



(VII)

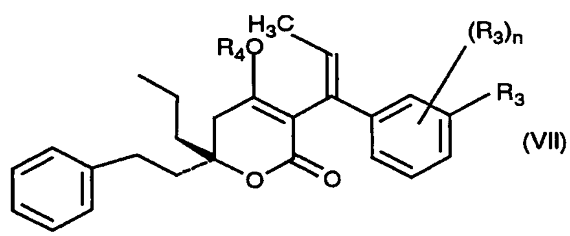
the E-geometrical isomer thereof or a mixture of the Z- and E-isomers, where R_3 and R_4 are as defined above, in the presence of catalyst containing Rh, a chiral ligand with at least one phosphorous atom where the hydrogenation is conducted in the presence of a base.

Also disclosed is a process for the preparation of a compound of the formula:



(VIII)

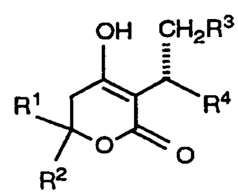
where R_3 and n are as defined above, where R_4 is selected from the group consisting of Na^+, K^+, Li^+, Cs^+ and $(R_{4-1})_4N^+$ where R_{4-1} are the same or different and are CH_3-, C_2H_5-, C_4H_9-, ϕ-CH_2- and C_8H_{17}- which comprises hydrogenating a compound of the formula:



(VII)

the E-geometrical isomer thereof or a mixture of the Z- and E-isomers in the presence of catalyst containing Rh, a chiral ligand with at least one phosphorous atom.

Additionally disclosed is a process for the preparation of a compound of the formula

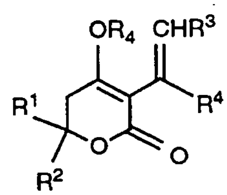


where R^1 and R^2 are the same or different groups and are each -H or up to 30 carbon atoms;

where R^3 is C_1-C_8 alkyl;

where R^4 is aryl optionally substituted by a functional group; and

where R_4 is -H or $-Si(CH_3)_3$ which comprises asymmetric hydrogenation of a compound of the formula



where R^1, R^2, R^3, R^4 and R_4 is as defined above in the presence of as a catalyst a complex of a transition metal and a chiral phosphine ligand with the proviso that when one of R^1 or R^2 is propyl, the other of R^1 or R^2 is not 1-(2-phenyl)ethyl.

DETAILED DESCRIPTION OF THE INVENTION

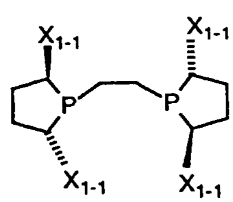
The present invention is an improved catalytic hydrogenation of the olefin (VII) to the corresponding chiral compound (VIII); the improvement is the addition of base or starting with the enolate. Another invention is the improved catalytic hydrogenation of the olefin where when one of R^1 or R^2 is propyl the other of R^1 or R^2 is not 1-(2-phenyl)ethyl.

It is preferred that the catalyst be the (2R,5R)-enantiomer of a catalyst of the formula:

$$X_1\text{-}Rh^+\text{-cyclooctadiene } X_2^-$$

where X_1 is selected from the group consisting of:

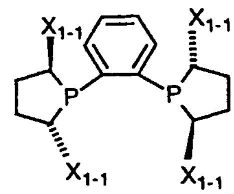
(1) BPE



BPE

where $X_{1\text{-}1}$ is $-CH_3$ or $-C_2H_5$,

(2) DuPHOS



DuPHOS

where X_{1-1} is as defined above;

where X_2 is selected from the group consisting of:

(1) BF_4^- and

(2) CF_3-CO-O^-.

It is preferred that the olefin used be a mixture of E/Z-isomers of (VII). It is preferred that n be 0. For the olefin (VII), R_3 is selected from the group consisting of :

-NO_2,

-NH_2,

-NH-SO_2-[4-trifluoromethylpyridin-2-yl],

-N(-CH_2-ϕ)$_2$,

-N(R_{3-1})(R_{3-2}) where R_{3-1} and R_{3-2} are the same or different and are:

-H,

-CO-O-(*t*-butyl),

-CO-O-CH_2-ϕ,

-CO-CH_3,

-CO-ϕ,

-Cl,

-Br,

-I,

-OH,

-O-SO_2-CF_3; it is preferred that R_3 is -NO_2, -NH_2 and -N(R_{3-1})(R_{3-2}) where one of R_{3-1} and R_{3-2} is -H and the other is -CO-O-(*t*-butyl); it is more preferred that R_3 is -NO_2. n is 0 or 1 with the provisos, (1) that when n is 0 the R_3 group must be in the meta position and (2) that when n is 1, one of R_3 must be -Cl, -Br, -I, -OH or -O-SO_2-CF_3. When

n is 0, the chiral compound (VIII) is represented with one R_3 group as (VIII-A) and when n is 1, the chiral compound (VIII) is represented with two R_3 groups as (VIII-B).

R_4 is selected from the group consisting of -H, $-Si(CH_3)_3$, Na^+, K^+, Li^+, Cs^+ and $(R_{4-1})_4N^+$ where R_{4-1} are the same or different and are CH_3-, C_2H_5-, C_4H_9-, ϕ-CH_2- and C_8H_{17}-. It is preferred that the compound (VIII) is [3α(R),6(R)]5,6-dihydro-4-hydroxy-3-[1-(3-nitrophenyl)propyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one.

The process of the present invention has two very similar forms. In the first form of the process, the olefin (VII) has at the 4-position the hydroxy functionality or a silylated ether derivative; R_4 is either -H or $-Si(CH_3)_3$. The alternative form starts with the enolate at C-4, where R_4 is a cation, Na^+, K^+, Li^+, Cs^+, $(R_{4-1})_4N^+$ where the R_{4-1} are the same or different and are CH_3-, C_2H_5-, C_4H_9-, ϕ-CH_2- and C_8H_{17}-.

When R_4 is either -H or $-Si(CH_3)_3$ the reaction requires a base. The operable bases are those where the base has a $pK_a > 5$; it is preferred that the base be selected from the group consisting of hydroxide, alkoxide where the alkyl group is from C_1-C_5, bicarbonate, carbonate, di- and tri-basic phosphate, borate, fluoride and $R_aR_bR_cN$ where R_a,, R_b and R_c are the same or different and are:

H-,

C_1-C_4 alkyl,

ϕ-,

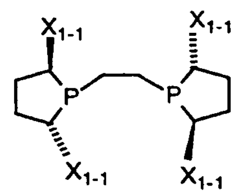
$R_dR_eR_fSi$- where the R_d, R_e and R_f are the same or different and are C_1-C_3 alkyl with the proviso that not more than one of the R_a,, R_b and R_c are H-; it is more preferred that the base be selected from the group consisting of hydroxide, methoxide, ethoxide, *t*-butoxide, *t*-amylate, *s*-butoxide, di- and tribasic phosphate and carbonate; it is even more preferred that the base be is methoxide or carbonate. The amount of base required is in an amount of less than one equivalent; it is preferred that the base be present in an amount of about 0.1 equivalents.

It is preferred that the catalyst containing Rh, a chiral ligand with at least one phosphorous atom, be a catalyst of the formula:

$$X_1\text{-}Rh^+\text{-cyclooctadiene}\ X_2^-$$

where X_1 is selected from the group consisting of:

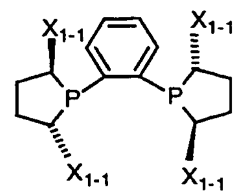
(1) BPE



BPE

where X_{1-1} is $-CH_3$ or $-C_2H_5$, and

(2) DuPHOS



DuPHOS

where X_{1-1} is as defined above; where X_2 is selected from the group consisting of BF_4^- and CF_3-CO-O^-. These catalysts are well known to those skilled in the art, see for example US Patents 5,171,892, 5,532,395 and 5,559,267. For the catalyst it is preferred that X_1 be of formula (2). It is also preferred that X_2 be BF_4^- and X_{1-1} be $-CH_3$. The amount of catalyst is expressed as a ratio (in moles) of substrate/catalyst. Operable ratios include where the ratio (in moles) of substrate/catalyst is from about 200/1 to 5,000/1; it is preferred that the ratio (in moles) of substrate/catalyst is from about 500/1 to 3,000/1; it is more preferred that the ratio (in moles) of substrate/catalyst is from about 1,000/1 to 2,000/1.

The process of the invention is performed in a temperature range of about 20° to about 120°; preferably in a temperature range of from about 40° to about 80°; more preferably in a temperature range of from about 50° to about 65°.

The process of the invention is performed under a pressure in the range of about from about 40 to about 1,000 psi; preferably in a range of about 70 to about 1,000 psi; more preferably in a range of from about 70 to about 90 psi. Alternatively the pressure can be expressed as kPa which is kiloPascals of hydrogen.

The solvent(s) utilized in the present invention are those well known to those skilled in the art for performing hydrogenation reactions and are not critical as long a the olefin (VII) is in solution. It is preferred that the solvent be methanol, ethanol, acetone, methylene chloride, ethyl acetate, acetonitrile, toluene. It is more preferred that the solvent be methanol or toluene.

When performing the process of the present invention, it is preferred to combine the olefin (VII), the base, solvent and hydrogen before adding the catalyst. It is even more preferred to combine all these reagents and bring the reaction mixture to reaction temperature prior to adding the catalyst.

For commercial reasons, the process of the present invention should be complete in less than 72 hours. Preferably the process is complete in about 24 to about 48 hours and have a selectivity of diastereomeric excess of about 80%, preferably a diastereomeric excess of greater than about 90%. It is realized that not all reactions conditions set for above will produce the desired results if the minimum of each range is selected. However, one skilled in the art is well aware of this and can select the optimum pressure to be used with the minimum temperature or the optimum temperature to be used with the minimum pressure, etc. It is preferred that when the temperature is about 20°, the pressure is at least about 150 psi or greater to complete the reaction in about 72 hr. If the temperature is about 20° and it is desired to complete the reaction in about 48 hr, about 200 psi is required . Likewise when the pressure is 40 psi, it is preferred that the temperature is 48° or greater to complete the reaction in 72 hr. If it is desired to complete the reaction in 48 hr, at least 58° is necessary.

The chiral compound (VIII-A or VIII-B) can be either isolated or carried on *in situ*. It is preferred that the chiral compound (VIII-A or VIII-B) be isolated in order to determine the diastereomeric purity of the product.

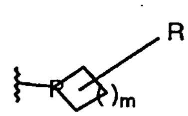
When R_4 is selected from the group consisting of Na^+, K^+, Li^+, Cs^+ and $(R_{4-1})_4N^+$ then the hydrogenation process does not require that any base be added.

When n is 0, R_3 must be in the *meta* position. The reason is in tipranavir the substituent on the phenyl ring is in the *meta* position. CHART B discloses the preferred process when n is 0. It is preferred that R_3 be $-NO_2$. Asymmetric hydrogenation of the olefin (VII) produces the chiral compound (VIII-A). When R_3 is $-NO_2$, it is next reduced (EXAMPLE 7) to the amino intermediate (IX) followed by formation of the sulfonamide tipranavir product (X) by the process of EXAMPLE 8. If R_3 is $-NH_2$, then the asymmetric hydrogenation of the olefin (VII) produces the amino intermediate (IX) directly. If R_3 is $NH-SO_2$-[4-trifluoromethylpyridin-2-yl], then the desired tipranavir (X) is produced directly. If R_3 is $-N(-CH_2-\phi)_2$ or $-N(R_{3-1})(R_{3-1})$ then the benzyl or R_{3-1} groups are removed as is known to those skilled in the art by hydrogenation (in the presence of a suitable supported transition metal catalyst, e.g. Pd/C) or by hydrolysis (treat with acids or bases in a suitable

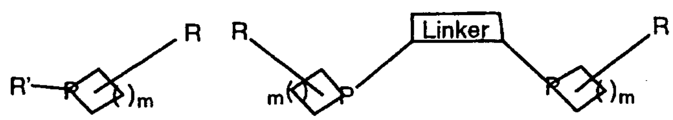
solvent) to cleave the benzyl or R_{3-1} groups to produce compound (IX). If R_3 is halogen then, compound (VII-A) can not be directly converted to compound (IX). It must first be converted to a compound where the halogen group is replaced by a non-halogen R_3 group. The compound containing the non-halogen R_3 group is then transformed to compound (IX). When R_3 is halogen in compound (VII-A) the halogen group is transformed to a non-halogen R_3 group by the action of a suitable transition metal catalyst in the presence of a suitable amine, such as dibenzylamine in a manners reviewed and described in *Angew. Chem. Int. Ed.* 37, 2046 (1998) to provide the intermediate compound (XI), where R_3 is -N(-$CH_2\phi)_2$ which is converted, as described previously to compound (IX). Other suitable amines include hexamethyldisilazane, producing an intermediate (XI), where R_3 is -N[$Si(CH_3)_3]_2$, which can be hydrolyzed to provide compound (IX). If R_3 is -O-SO_2-CF_3 then compound (VII-A) one skilled in the art would know that this compound could converted to compound (IX) in manner similar to when R_3 is halogen. If R_3 is -OH, then one skilled in the art would first convert the -OH to -O-SO_2-CF_3 or similar sulfonate ester, and then proceed to compound (IX) in the manner described for those compounds.

CHART C discloses the invention when n is 1. When n is 1, one of the R_3 groups must be in the *meta* position. The other R_3 group need not be in the *meta* position. When n is 1, one of the R_3 groups must be -Cl, -Br, -I, -OH or -O-SO_2-CF_3. It is this R_3 group, -Cl, -Br, -I, -OH or -O-SO_2-CF_3 which does not have to be in the *meta* position. The nitrogen functionality of R_3 must be in the *meta* position. The second R_3 group can remain on during the hydrogenation of the olefin (VII) to the chiral compound (VIII) and then would be removed in a subsequent reaction leaving the chiral compound (VIII) or the amino intermediate (IX) with just the one R_3 group in the desired meta position.

The other process of the invention is the improved catalytic hydrogenation of the olefin where when one of R^1 or R^2 is propyl, the other of R^1 or R^2 is not 1-(2-phenyl)ethyl. This proviso is to expressly exclude the compound formula (VIII), [3α(R),6(R)]5,6-dihydro-4-hydroxy-3-[1-(3-nitrophenyl)propyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one. This process is practiced analogously. For this process it is preferred that the catalyst has for the chiral phosphine ligand the following group:

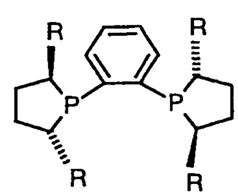


where m is 0 or an integer from 1 to 6, and R represents at least one non-hydrogen organic group of up to 30 carbon atoms. It is more preferred that the ligand is of the following formulas, where Linker and R' are independently any non-hydrogen organic group of up to 30 carbon atoms.

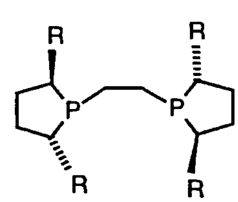


It is preferred that R^1 is C_6-C_{15} arylalkyl; it is more preferred that R^1 is phenylethyl. It is preferred that R^2 is C_1-C_8 alkyl; it is more preferred that R^2 is *n*-propyl. It is preferred that R^3 is methyl and R^4 is phenyl substituted by a functional group. It is preferred that the functional group is $-NO_2$.

It is preferred that the ligand is a chiral bis-phosphine of 1,2-bis(phospholano)benzene (DuPHOS) or 1,2-bis(phospholano)ethane (BPE) of the respective formulas:



DuPHOS



BPE

or the opposite enantiomer thereof, where each R is any non-hydrogen organic group. It is preferred that each R is C_1-C_4 linear or branched alkyl group. It is preferred that the

transition metal is Rh, Ru or Ir; it is more preferred that the transition metal be Rh. With regard to base it is preferred that the amount of base be a catalytic quantity; it is preferred that the base is NaOMe or Na_2CO_3. It is preferred that the reaction temperature be 0-125°C; more preferably 25-75°C. It is preferred that the reaction pressure is 35 to 14,000 kPa H_2, more preferably 350 to 1,400 kPa H_2 and even more preferably 500 to 700 kPa H_2. It is preferred the reaction is conducted in a solvent that is methanol or toluene. It is preferred that the catalyst is 0.1 mole % [((R,R)-Me-DUPHOS)Rh(COD)]BF_4. with 10% mole % Na_2CO_3 co-catalyst, the temperature is 50 to 60°C, the pressure is 500 to 700 kPa H_2 and the solvent is methanol. It is also preferred that the product be crystallized from aqueous methanol which enriches the diastereomeric excess of the product.

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

I. CONVENTIONS FOR FORMULAS AND DEFINITIONS OF VARIABLES

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a numerical subscript, for example, "Z_1" or "R_i" where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the formula by one or two chemical bonds. For example, a group Z_1 would represent a bivalent variable if attached to the formula CH_3-C(=Z_1)H. Groups R_i and R_j would represent monovalent variable substituents if attached to the formula CH_3-CH_2-C(R_i)(R_j)-H. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed in parenthesis. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left which is not enclosed in parentheses. Thus, in the formula above, both R_i and R_j are bonded to the preceding carbon atom. Also, for any molecule with an established system of carbon atom numbering, such as steroids, these carbon atoms are designated as C_i, where "i" is the integer corresponding to the carbon atom number. For example, C_6 represents the 6 position or carbon atom number in the steroid nucleus as traditionally designated by those skilled in the art of steroid chemistry.

Likewise the term "R_6" represents a variable substituent (either monovalent or bivalent) at the C_6 position.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus CH_3-O-CH_2-CH(R_i)-CH_3 represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., CH_2=C(R_i)-O-CH_3, and the symbol "≡" represents a triple bond, e.g., HC≡C-CH(R_i)-CH_2-CH_3. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)-, with the former being preferred for simplicity.

A rigid cyclic (ring) structure for any compounds herein defines an orientation with respect to the plane of the ring for substituents attached to each carbon atom of the rigid cyclic compound. For saturated compounds which have two substituents attached to a carbon atom which is part of a cyclic system, -C(X_1)(X_2)- the two substituents may be in either an axial or equatorial position relative to the ring and may change between axial/equatorial. However, the position of the two substituents relative to the ring and each other remains fixed. While either substituent at times may lie in the plane of the ring (equatorial) rather than above or below the plane (axial), one substituent is always above the other. In chemical structural formulas depicting such compounds, a substituent (X_1) which is "below" another substituent (X_2) will be identified as being in the alpha (α) configuration and is identified by a broken, dashed or dotted line attachment to the carbon atom, i.e., by the symbol "- - -" or "...". The corresponding substituent attached "above" (X_2) the other (X_1) is identified as being in the beta (ß) configuration and is indicated by an unbroken or solid line attachment to the carbon atom.

When a variable substituent is bivalent, the valences may be taken together or separately or both in the definition of the variable. For example, a variable R_i attached to a carbon atom as -C(=R_i)- might be bivalent and be defined as oxo or keto (thus forming a carbonyl group (-CO-) or as two separately attached monovalent variable substituents a-R_{i-j} and ß-R_{i-k}. When a bivalent variable, R_i, is defined to consist of two monovalent variable substituents, the convention used to define the bivalent variable is of the form "a-R_{i-j}:ß-R_{i-k}" or some variant thereof. In such a case both a-R_{i-j} and ß-R_{i-k} are attached to the carbon atom to give -C(a-R_{i-j})(ß-R_{i-k})-. For example, when the bivalent variable R_6, -C(=R_6)- is defined to consist of two monovalent variable substituents, the two monovalent variable substituents are a-R_{6-1}:ß-R_{6-2}, ... a-R_{6-9}:ß-R_{6-10}, etc, giving -C(a-R_{6-1})(ß-R_{6-2})-, ... -C(a-R_{6-}

$_9$)(ß-$R_{6\text{-}10}$)-, etc. Likewise, for the bivalent variable R_{11}, -C(=R_{11})-, two monovalent variable substituents are a-$R_{11\text{-}1}$:ß-$R_{11\text{-}2}$. For a ring substituent for which separate a and ß orientations do not exist (e.g. due to the presence of a carbon carbon double bond in the ring), and for a substituent bonded to a carbon atom which is not part of a ring the above convention is still used, but the a and ß designations are omitted.

Just as a bivalent variable may be defined as two separate monovalent variable substituents, two separate monovalent variable substituents may be defined to be taken together to form a bivalent variable. For example, in the formula -$C_1(R_i)H$-$C_2(R_j)H$- (C_1 and C_2 define arbitrarily a first and second carbon atom, respectively) R_i and R_j may be defined to be taken together to form (1) a second bond between C_1 and C_2 or (2) a bivalent group such as oxa (-O-) and the formula thereby describes an epoxide. When R_i and R_j are taken together to form a more complex entity, such as the group -X-Y-, then the orientation of the entity is such that C_1 in the above formula is bonded to X and C_2 is bonded to Y. Thus, by convention the designation "... R_i and R_j are taken together to form -CH_2-CH_2-O-CO- ..." means a lactone in which the carbonyl is bonded to C_2. However, when designated "... R_j and R_i are taken together to form -CO-O-CH_2-CH_2-the convention means a lactone in which the carbonyl is bonded to C_1.

The carbon atom content of variable substituents is indicated in one of two ways. The first method uses a prefix to the entire name of the variable such as "C_1-C_4", where both "1" and "4" are integers representing the minimum and maximum number of carbon atoms in the variable. The prefix is separated from the variable by a space. For example, "C_1-C_4 alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given). Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined. Thus C_2-C_4 alkoxycarbonyl describes a group CH_3-$(CH_2)_n$-O-CO- where n is zero, one or two. By the second method the carbon atom content of only each portion of the definition is indicated separately by enclosing the "C_i-C_j" designation in parentheses and placing it immediately (no intervening space) before the portion of the definition being defined. By this optional convention (C_1-C_3)alkoxycarbonyl has the same meaning as C_2-C_4 alkoxycarbonyl because the "C_1-C_3" refers only to the carbon atom content of the alkoxy group. Similarly while both C_2-C_6 alkoxyalkyl and (C_1-C_3)alkoxy(C_1-C_3)alkyl define alkoxyalkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

When the claims contain a fairly complex (cyclic) substituent, at the end of the phrase naming/designating that particular substituent will be a notation in (parentheses) which will correspond to the same name/designation in one of the CHARTS which will also set forth the chemical structural formula of that particular substituent.

II. DEFINITIONS

All temperatures are in degrees Centigrade.

TLC refers to thin-layer chromatography.

HPLC refers to high pressure liquid chromatography.

THF refers to tetrahydrofuran.

CDI refers to 1,1'-carbonyldiimidazole.

Saline refers to an aqueous saturated sodium chloride solution.

IR refers to infrared spectroscopy.

CMR refers to C-13 magnetic resonance spectroscopy, chemical shifts are reported in ppm (d) downfield from TMS.

NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (d) downfield from tetramethylsilane.

-ϕ refers to phenyl (C_6H_5).

MS refers to mass spectrometry expressed as m/e, m/z or mass/charge unit. $[M + H]^+$ refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

psi refers to pounds per ft^2.

kPa refers to kiloPascals of hydrogen.

The "chiral compound (VIII)" includes both the chiral compound with one R_3 group (VIII-A) and with two R_3 groups (VIII-B).

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

EXAMPLE 1 Ethyl-3-hydroxy-3-(2-phenylethyl)hexanoate (II)

To a solution of diisopropylamine (32.2 ml, 230 mmol) in tetrahydrofuran (240 ml) at -58° is added 2.63 M n-butyl lithium in hexane (87.4 ml, 230 mmol) over one hour. Ethyl acetate (21.4 ml, 220 mmol) is then added and the reaction mixture stirred for 1 hour during which time the reaction mixture was cooled to -70°. 1-Phenyl-3-hexanone (I, 35.2 g, 200 mmol) is added slowly over 30 minutes and the reaction mixture stirred cold for 1 hour. The mixture was quenched with aqueous ammonium chloride (100 ml) and warmed to 20-25°. The mixture is then acidified with hydrochloric acid (4 M). The desired product is extracted into methyl *t*-butyl ether dried over magnesium sulfate and concentrated to give the title compound, TLC $R_f = 0.71$ (ethyl acetate/hexane, 30/70); NMR ($CDCl_3$) 7.28-7.12, 4.13, 3.60, 2.73-2.63, 2.50, 1.83-1.77, 1.58-1.53, 1.41-1.36, 1.24 and 0.93 L; CMR ($CDCl_3$) 173.0, 143.2, 128.5, 128.4, 128.3, 128.1, 125.8, 72.8, 60.6, 42.9, 41.3, 30.1, 17.0, 14.6 and 14.2 L; MS (CI, ammonia) m/z (relative intensity) 282 (100), 264 (63), 247 (10), 194 (13), 172 (5), 159 (5).

EXAMPLE 2 3-Hydroxy-3-(2-phenylethyl)hexanoic acid (III)

Ethyl-3-hydroxy-3-(2-phenylethyl)hexanoate (II, EXAMPLE 1, 200 mmol) is dissolved in methanol (423 ml) and 2M sodium hydroxide (150 ml, 300 mmol) is added. The reaction mixture is stirred at 20-25° overnight. Methanol is removed and the remaining aqueous mixture is acidified with hydrochloric acid (4 M). The desired product is extracted into methyl *t*-butyl ether and dried over magnesium sulfate. The product is concentrated to give the title compound, TLC $R_f = 0.10$ (ethyl acetate/hexane, 30/70); NMR ($CDCl_3$) 7.43-7.13, 2.77-2.62, 2.06, 1.87-1.76, 1.63-1.57, 1.45-1.31 and 0.93 L; CMR ($CDCl_3$) 176.9, 141.9, 128.4, 128.3, 125.9, 73.4, 42.7, 41.4, 40.9, 31.9, 17.0 and 14.5 L; MS (CI, ammonia) m/z (relative intensity) 254 (100), 236 (28), 218 (3), 194 (3), 159 (5).

EXAMPLE 3 R-3-Hydroxy-3-(2-phenylethyl)hexanoic acid, (1R,2S)-norephedrine salt (IV)

3-Hydroxy-3-(2-phenylethyl)hexanoic acid (III, EXAMPLE 2, 2.83 g, 11.97 mmol adjusted for methyl *t*-butyl ether) is dissolved in acetonitrile (15 ml). (1R,2S)-Norephedrine (910 mg, 5.99 mmol, 0.5 equiv.) is added and the mixture stirred overnight at 20-25°. After approximately one hour, the product began to precipitate. The following morning the slurry was cooled to 0° for 1 hour before filtering to collect the hydroxyacid salt. The cake is washed with acetonitrile (9 ml cold) and dried under reduced pressure with heat to give the desired product.

This material (ca. 1.5 g) is slurried in acetonitrile (21 ml) and heated to 70° for 30 minutes. The resulting solution is gradually cooled to 20-25° as the product precipitates. After 2 hours at 20-25°, the product is collected by vacuum filtration, washed with acetonitrile (21 ml) and dried at 20-25° under reduced pressure.

Again, this material is slurried in acetonitrile (21 ml) and heated to 70° for 30 minutes. The resulting solution is gradually cooled to room 20-25° as the product precipitates. After 2 hours at 20-25°, the product is collected by vacuum filtration, washed with acetonitrile (21 ml) and dried at 20-25° under reduced pressure to give the title compound, mp = 113-117°; NMR (methanol) 7.41-7.08, 5.18, 4.98, 3.15, 2.65-2.60, 2.34, 1.79-1.73, 1.56-1.52, 1.43-1.37, 1.06 and 0.92 L; CMR (methanol) 181.4, 144.6, 142.2, 130.2-129.3, 127.6, 127.1, 74.5, 73.9, 54.0, 46.4, 43.6, 43.4, 31.9, 31.9, 18.6, 15.7 and 12.9 L; MS (CI, ammonia) m/z (relative intensity) 388 (25), 303 (15), 254 (30), 236 (7), 152 (100); $[I]^{25}{}_{D}$ = 16 (C = 1.0, methanol).

EXAMPLE 4 (6R)-5,6-Dihydro-4-hydroxy-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VI)

R-3-Hydroxy-3-(2-phenylethyl)hexanoic acid, (1R,2S)-norephedrine salt (IV, EXAMPLE 3, 81 g, 209 mmol) is converted to the free acid, R-3-hydroxy-3-(2-phenylethyl)hexanoic acid by slurring the salt in ethyl acetate (810 ml) and adding hydrochloric acid (1 M, 810 ml). The free acid is extracted into the ethyl acetate and the ethyl acetate layer collected and concentrated to an oil. The free acid is then redissolved in tetrahydrofuran (490 ml) and the solution cooled to -10°. Carbonyl-diimidazole (37.3 g, 230 mmol) is added and the reaction mixture stirred cold for 2 hours. Monoethyl malonate magnesium salt (65.9 g, 230 mmol) is added and the reaction mixture gradually warmed to 20-25° while stirring overnight. The reaction is quenched with hydrochloric acid (1 M, 490 ml) and the organic layer collected. The organic layer is washed with a sodium bicarbonate solution and concentrated to 294 ml containing R-ethyl 5-hydroxy-7-phenyl-5-propylheptanoate (V). A solution of sodium hydroxide (0.5 M, 460 ml, 230 mmol) is added to the concentrated solution and the resulting cloudy mixture stirred at 20-25° overnight. Methyl *t*-butyl ether is added and the aqueous layer collected. The aqueous phase is acidified with hydrochloric acid (4 M) and the product is extracted into methyl *t*-butyl ether. The methyl *t*-butyl ether layer is dried over sodium sulfate and concentrated to give the title compound, TLC R_f = 0.22 (ethyl acetate/hexane, 50/50); NMR ($CDCl_3$) 7.29-7.13, 3.39, 2.70, 2.71-2.62, 1.98-1.93, 1.74-1.66, 1.45-1.34 and 0.93 L; CMR ($CDCl_3$) 176.89, 167.5, 140.4, 128.6, 128.4, 128.2, 128.2, 126.3, 83.2, 60.1, 47.1, 44.3, 40.7, 40.4, 29.6, 16.8 and

14.5 L; MS (CI, ammonia) m/z (relative intensity) 278 (100), 254 (15), 236 (15), 217 (5), 195 (5), 159 (3).

EXAMPLE 5 [3α(R),6(R)]5,6-Dihydro-4-hydroxy-3-[(Z)-1-(3-nitrophenyl)propenyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VII, major component) and [3α(R),6(R)]5,6-dihydro-4-hydroxy-3-[(E)-1-(3-nitrophenyl)propenyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VII, minor component)

(6R)-5,6-dihydro-4-hydroxy-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VI, EXAMPLE 4, 50.0 g, 187 mmol) is combined with m-nitropropiophenone (33.5 g, 187.2 mmol) and 375 ml of THF. Pyridine is added (31.0 mL, 374 mmol), and the resultant mixture is stirred and cooled to below -5. A solution is prepared by adding titanium tetrachloride (31 ml, 280 mmol) to 80 ml of toluene, and this solution is added to the mixture in a controlled manner to maintain the reaction temperature below 10°. Toluene (15 ml) is used to rinse in all of the titanium tetrachloride solution and at the end of this addition, the reaction mixture is warmed to between 35-45° and maintained in this range for about 16 hours. The reaction mixture is cooled to 0° and water (200 ml) is added in a single portion. This mixture is stirred until all solids dissolve. The mixture is warmed to at least 15° and then transferred to a separatory funnel using water (250 ml) and ethyl acetate (500 ml) to dilute the mixture. The aqueous layer is separated, removed, extracted with ethyl acetate (150 ml) and discarded. The primary organic layer is washed sequentially with hydrochloric acid (1 N, 2 x 150 ml), water (150 ml) and saturated sodium bicarbonate (150 ml). Each wash is extracted with the ethyl acetate (150 ml) extract prior to disposal. At this point the primary organic layer and the extract are combined and concentrated under reduced pressure to give a concentrate. The concentrate is then dissolved in methylene chloride (350 ml). This solution is extracted with a total of 500 ml of 1 N sodium hydroxide (4 x 50 ml, then 3 x 100 ml). The combined aqueous extracts are washed with a total of 500 ml of methylene chloride (4 x 50 ml, then 3 x 100 ml) and then treated with hydrochloric acid (3 N, 150 ml). The acidified mixture is extracted with methylene chloride (400 ml, then 6 x 100 ml) and the combined organic extracts are washed with water (200 ml) and then saline (200 ml). After drying further with anhydrous sodium sulfate, the mixture is filtered through a pad of magnesol and then concentrated under reduced pressure to give the mixture of title compounds, TLC R_f = 0.18 for (Z)-isomer, 0.28 for (E)-isomer (ethyl acetate/hexane, 1/1); CMR ($CDCl_3$) 166.93, 166.53, 148.27, 142.53, 142.39, 140.96, 132.23, 132.12, 131.82,

131.74, 129.87, 129.12, 128.55, 128.14, 126.16, 121.67, 120.56, 101.09, 81.77, 39.78, 35.23, 29.73, 16.91, 15.75, 15.69 and 14.23 L; MS (CI + NH_3) m/z (relative intensity) 439 (100), 422 (18), 409 (9), 392 (9), 278 (9), 194 (10), 136 (9).

EXAMPLE 6 [3α(R),6(R)]5,6-dihydro-4-hydroxy-3-[1-(3-nitrophenyl)propyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VIII)

[3α(R),6(R)]5,6-Dihydro-4-hydroxy-3-[(Z)-1-(3-nitrophenyl)propenyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VII, EXAMPLE 5, 4.24 g, 10 mmol) and [(1,5-cyclooctadiene)rhodium(I)-1,2-bis-(2R,5R)-dimethyl-phospholano)benzene]-tetrafluoroborate (6.0 mg, 0.01 mmol) are combined in an inert atmosphere and dissolved in 20 ml of deoxygenated methanol. The atmosphere is replaced with hydrogen at a pressure of 80 psig or more and the reaction is warmed to 55° and stirred for 24 hours. At the end of this period, the reaction is cooled to 20-25° and the hydrogen is replaced with an inert atmosphere. The reaction mixture is concentrated under reduced pressure and the residue is crystallized from a methanol/water mixture (3/1) to give the title compound, TLC $R_f = 0.49$ (ethyl acetate/hexanes, 1/1); HPLC rt = 6.93 min; NMR ($CDCl_3/CD_3OD$, 1/1) 8.08, 7.80, 7.56, 7.22, 7.07-6.88, 3.98, 3.33-3.30, 2.50-2.37, 1.92-1.70, 1.58-1.50, 1.22-1.14, 0.76 and 0.72 L; CMR ($CDCl_3/CD_3OD$, 1/1) 169.05, 166.66, 148.66, 147.79, 141.99, 135.30, 129.21, 129.02, 128.70, 126.55, 123.51, 121.23, 105.13, 81.39, 42.58, 40.39, 40.09, 36.76, 30.38, 24.95, 17.44, 14.54 and 13.04 L.

EXAMPLE 7 [3α(R),6(R)]3-[1-(3-Aminophenyl)propyl]-5,6-dihydro-4-hydroxy-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (IX)

To a solution of [3α(R),6(R)]5,6-dihydro-4-hydroxy-3-[1-(3-nitrophenyl)propyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VIII, EXAMPLE 6, 0.6993 g, 1.651 mmol) in THF (50 ml) is added palladium on carbon (5%, 50% water wet, 0.2574 g, 0.06048 mmol, 0.0366 equiv) and the mixture hydrogenated at 50 psi on a Parr shaker for 21 hrs. Celite (2.07 g) is added and the catalyst removed by vacuum filtration and rinsed with THF. The filtrate is concentrated to give the title compound, TLC $R_f = 0.45$ (ethyl acetate/hexanes, 1/1); HPLC rt = 5.18 min.

EXAMPLE 8 [R-(R*,R*)]-N-[3-[1-[5,6-dihydro-4-hydroxy-2-oxo-6-(2-phenylethyl)-6-propyl-2H-pyran-3-yl]propyl]phenyl]-5-(trifluoromethyl)-2-pyridinesulfonamide (X)

To a mixture of [3α(R),6(R)]3-[1-(3-aminophenyl)propyl]-5,6-dihydro-4-hydroxy-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (IX, EXAMPLE 7, crude 0.555 g, 1.378

mmol based on title compounds XIX), in methylene chloride (3.10 ml), DMSO (0.100 ml, 1.409 mmol, 1.02 equiv) and pyridine (0.56 ml, 6.92 mmol, 5.02 equiv) is added the crude mixture of 5-(trifluoromethyl)-2-pyridinesulfonyl chloride in methylene chloride prepared above (5.23 ml, ~2.3 mmol based on thiol, ~1.7 equiv) at -25 to -30° over 2 hours, titrating with the 5-(trifluoromethyl)-2-pyridinesulfonyl chloride mixture to an HPLC endpoint of 1.4 area % residual [3α(R),6(R)]3-[1-(3-aminophenyl)propyl]-5,6-dihydro-4-hydroxy-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one. Aqueous hydrochloric acid (1 M, 6.2 ml, 6.2 mmol, 4.50 equiv) and ethyl acetate (5.2 ml) is added and the phases separated. The aqueous phase is washed with methylene chloride (10 ml) and the combined organic phases dried on magnesium sulfate and concentrated. This concentrate is loaded on a silica gel column (9.76 g silica gel) packed with ethyl acetate/hexanes (10/90) and the product eluted with the following ethyl acetate in hexanes mixtures (50 ml 10%, 100 ml 20%, 100 ml 30%, and 50 ml 40%). The eluent is combined and concentrated to an oil with an ethyl acetate chase. Ethyl acetate is added (5.2 ml) and the product precipitated by slow addition of heptane (15 ml). The resultant slurry is cooled to -30° and the precipitate collected by vacuum filtration, washed with a -30° mixture of ethyl acetate (1 ml) and heptane (4 ml) and dried in a nitrogen stream to give the title compound, mp = 86-89/; TLC R_f = 0.66 (ethyl acetate/hexane, 50/50); NMR (CD_3OD) 8.94, 8.19, 8.02, 7.25-6.97, 3.93, 2.68-2.52, 2.15-2.09, 1.96-1.64, 1.33, 0.88 and 0.83 L; CMR (CD_3OD) 169.9, 167.0, 161.6, 148.1, 147.6, 142.8, 137.7, 137.0, 130.1, 129.5, 129.3, 127.0, 126.1, 124.2, 122.6, 120.3, 106.2, 81.9, 43.6, 40.5, 40.5, 37.4, 30.9, 25.8, 17.9, 14.7 and 13.3 L; MS (CI, ammonia) m/z (relative intensity) 621 (1.7), 620 (5.4), 604 (1.1), 603 (3.4), 411 (12), 394 (12), 148 (100); IR (mull) 1596, 1413, 1359, 1326, 1177, 1149, 1074 and 720 cm^{-1} (same solid state form as reference).

EXAMPLE 9 [3α(R),6(R)]5,6-Dihydro-4-hydroxy-3-[1-(3-nitrophenyl)propyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VIII)

[3α(R),6(R)]5,6-Dihydro-4-hydroxy-3-[(Z)-1-(3-nitrophenyl)propenyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VII, EXAMPLE 5, 1.0 g, 2.37 mmol) and sodium carbonate (0.025 g, 0.23 mmol) are placed in a 50 ml Parr pressure vessel which is then purged with hydrogen (by pressurization and venting four times with 70 psi hydrogen). To this mixture is added degassed methanol (4.5 ml), which was degassed by nitrogen bubbling for 2 to 3 hr with stirring at 20-25° . The vessel is again Purged with hydrogen (by pressurization and venting two times with 70 psi hydrogen). The reactor is charged to 70

psi hydrogen and heated to an internal temperature of about 50° (resulting in an internal pressure of abut 80 psi). Upon reaching the required temperature, the vessel is de-pressurized and a mixture of [(1,5-cyclooctadiene)rhodium(I)-1,2-bis-(2R,5R)-dimethyl-phospholano)benzene]tetrafluoroborate (1.4 mg, 2.3 mmol) in degassed methanol (0.5 ml) is added. The vessel is then re-pressurized to 80 psi and heated at 55-60°. After stirring for 22 hr. the vessel is vented into a fume hood. After transfer to a round bottom flask, the solvent is remove under reduced pressure. The residue is partitioned between methylene chloride (10 ml) and hydrochloric acid (2 M, 10 ml). The organic phase is separated, washed with saline (10 ml), dried over magnesium sulfate, filtered and concentrated under reduced pressure to give the title compound. The product is analyzed by NMR (200 Mhz, CD_3OD) and by chiral Super Critical Fluid Chromatography 20 min retention time.

EXAMPLE 10 [3α(R),6(R)]5,6-dihydro-4-hydroxy-3-[1-(3-nitrophenyl)propyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VIII)

Following the general procedure of EXAMPLE 9 and making non-critical variations, but performing the reaction at 20-25°, at 200 psi, with a catalyst loading (mol %) of 0.1 and using no base, the title compound is not observed in 2 hr and is obtained in 5% in 48 hr.

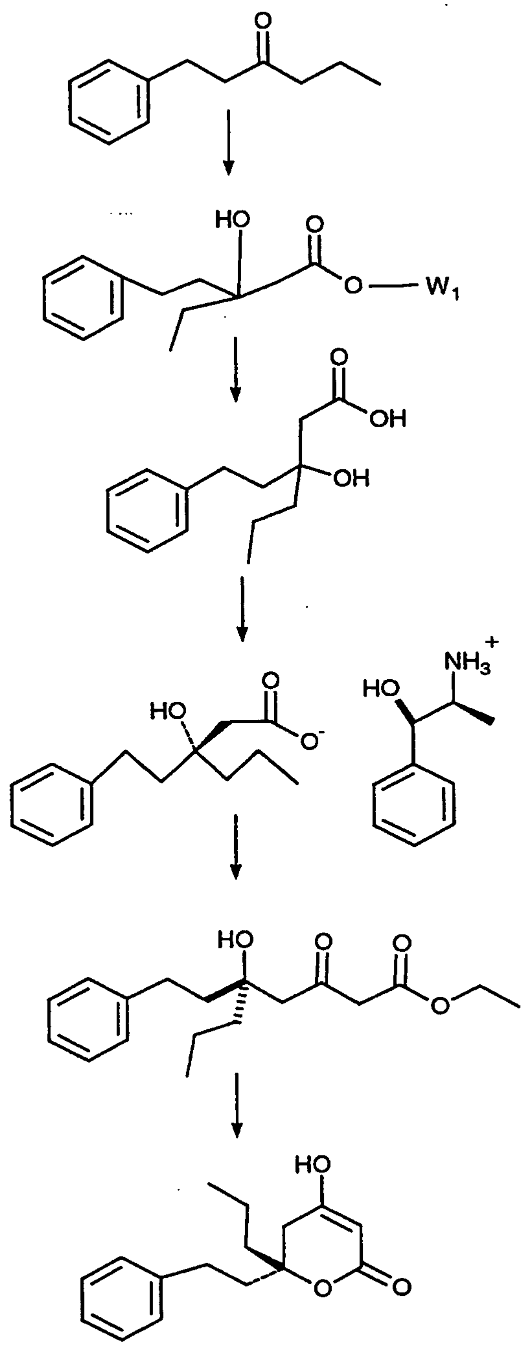
EXAMPLE 11 [3α(R),6(R)]5,6-dihydro-4-hydroxy-3-[1-(3-nitrophenyl)propyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VIII)

Following the general procedure of EXAMPLE 9 and making non-critical variations, but performing the reaction at 20-25°, at 200 psi, with a catalyst loading (mol %) of 0.1 and using sodium methoxide (1 equivalent), the title compound is observed in trace amounts in 2 hr; in 35% in 21 hr and in 100% in 96 hr with an enantiomeric purity of 88.7%.

EXAMPLE 12 [3α(R),6(R)]5,6-dihydro-4-hydroxy-3-[1-(3-nitrophenyl)propyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one (VIII)

Following the general procedure of EXAMPLE 9 and making non-critical variations, but performing the reaction at 20-25°, at 200 psi, with a catalyst loading (mol %) of 0.1 and using sodium methoxide (0.1 equivalent), the title compound is observed in trace amounts in 2 hr; in 60% in 24 hr and in 100% in 96 hr with an enantiomeric purity of 94.3%.

CHART A



(I)

(II)

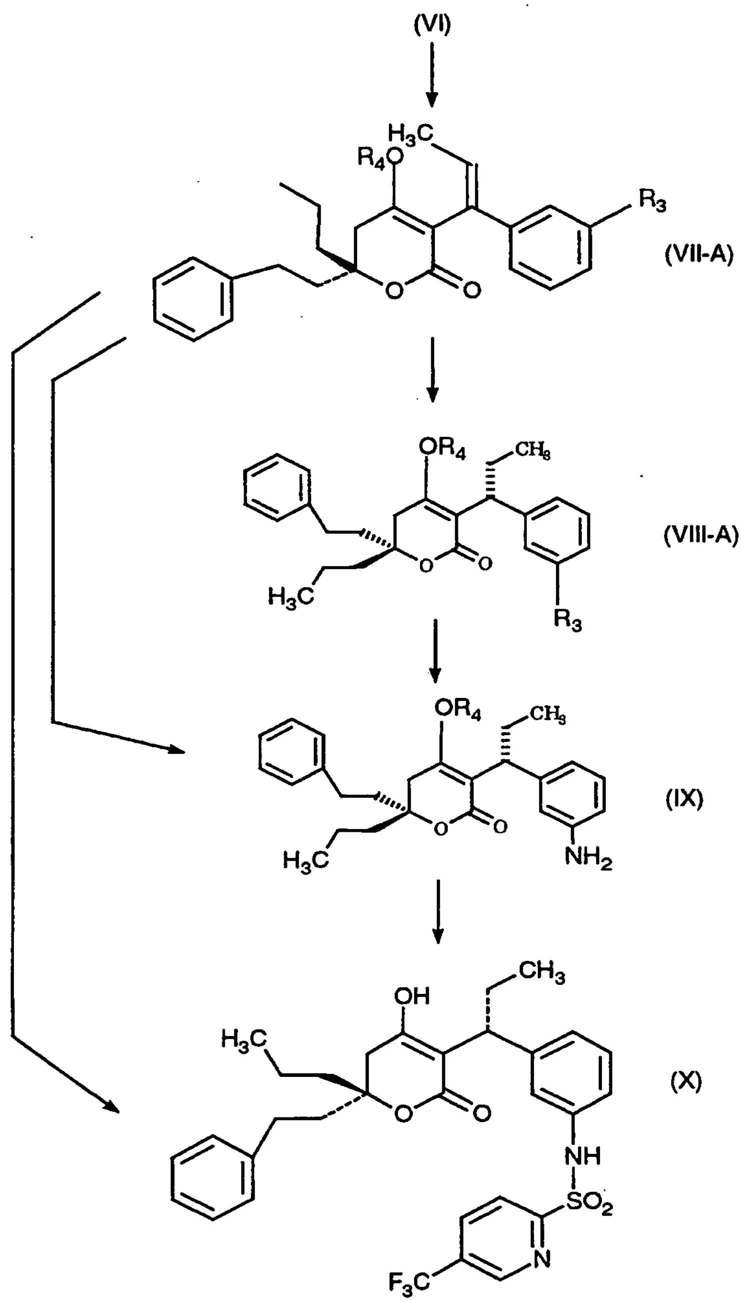
(III)

(IV)

(V)

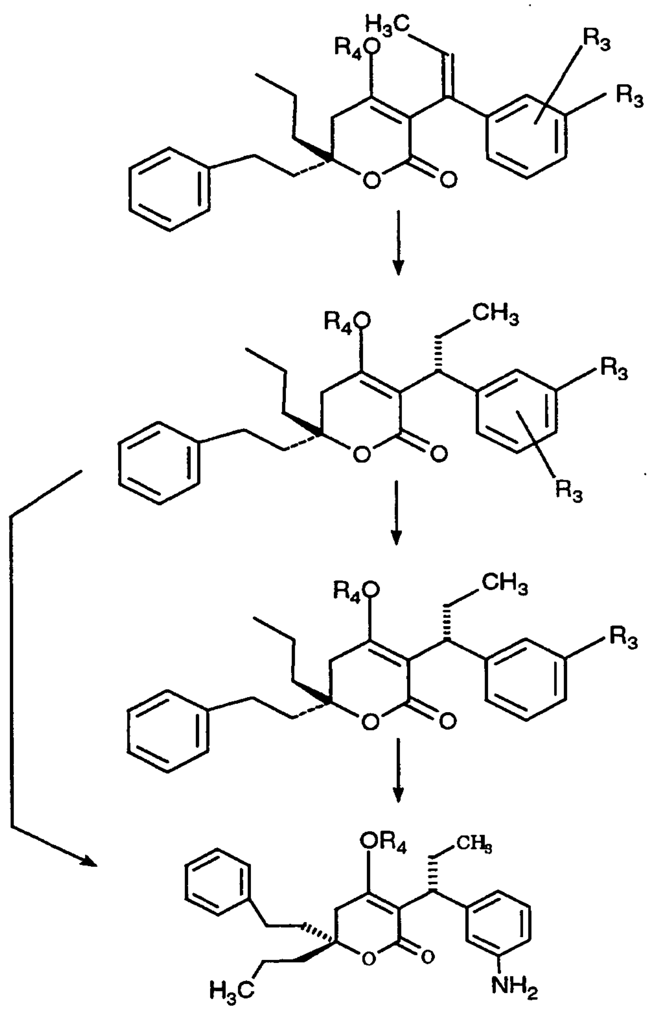
(VI)

CHART B



(VI)
H_3C
R_4O
R_3
(VII-A)
OR_4
CH_3
H_3C
R_3
(VIII-A)
OR_4
CH_3
H_3C
NH_2
(IX)
OH
CH_3
H_3C
NH
SO_2
N
F_3C
(X)

CHART C



(VII-B)

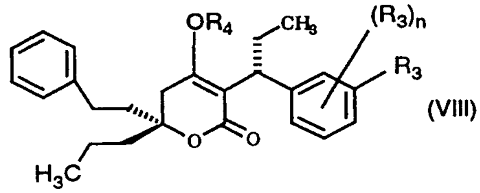
(VIII-B)

(XI)

(IX)

CLAIMS

1. A process for the preparation of a compound of the formula:

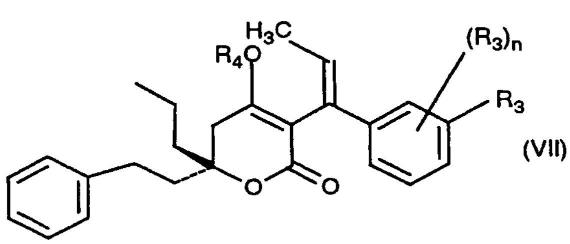


(VIII)

where R_3 is selected from the group consisting of :

- $-NO_2$,
- $-NH_2$,
- $-NH-SO_2-$[4-trifluoromethylpyridin-2-yl],
- $-N(-CH_2-\phi)_2$,
- $-N(R_{3-1})(R_{3-2})$ where R_{3-1} and R_{3-2} are the same or different and are:
  - -H,
  - -CO-O-(*t*-butyl),
  - $-CO-O-CH_2-\phi$,
  - $-CO-CH_3$,
  - $-CO-\phi$,
- -Cl,
- -Br,
- -I,
- -OH,
- $-O-SO_2-CF_3$,

where n is 0 or 1 with the provisos, (1) that when n is 0 the R_3 group must be in the meta position and (2) that when n is 1, one of R_3 must be -Cl, -Br, -I, -OH or $-O-SO_2-CF_3$, where R_4 is selected from the group consisting of -H and $-Si(CH_3)_3$, which comprises hydrogenating a compound of the formula:



(VII)

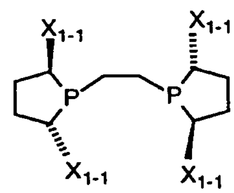
the E-geometrical isomer thereof or a mixture of the Z- and E-isomers, where R_3 and R_4 are as defined above, in the presence of catalyst containing Rh, a chiral ligand with at least one phosphorous atom where the hydrogenation is conducted in the presence of a base.

2. A process according to claim 1 where the catalyst is the (2R,5R)-enantiomer of a catalyst of the formula:

X_1-Rh^+-cyclooctadiene X_2^-

where X_1 is selected from the group consisting of:

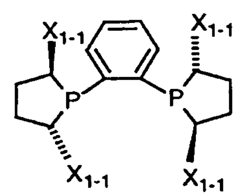
(1) BPE



BPE

where X_{1-1} is $-CH_3$ or $-C_2H_5$,

(2) DuPHOS



DuPHOS

where X_{1-1} is as defined above;

where X_2 is selected from the group consisting of:

(1) BF_4^- and

(2) CF_3-CO-O^-.

3. A process according to claim 1 where a mixture of E/Z-isomers of (VII) is used.

4. A process according to claim 1 where n is 0.

5. A process according to claim 1 where R_3 is $-NO_2$, $-NH_2$ and $-N(R_{3-1})(R_{3-2})$ where one of R_{3-1} and R_{3-2} is -H and the other is -CO-O-(*t*-butyl).

6. A process according to claim 5 where R_3 is $-NO_2$.

7. A process according to claim 1 where R_4 is -H.

8. A process according to claim 1 where the base has a $pK_a > 5$.

9. A process according to claim 1 where the base is selected from the group consisting of hydroxide, alkoxide where the alkyl group is from C_1-C_5, bicarbonate, carbonate, di- and tri-basic phosphate, borate, fluoride and $R_aR_bR_cN$ where R_a, R_b and R_c are the same or different and are:

H-,

C_1-C_4 alkyl,

ϕ-,

$R_dR_eR_fSi$- where the R_d, R_e and R_f are the same or different and are C_1-C_3 alkyl with the proviso that not more than one of the R_a, R_b and R_c are H-.

10. A process according to claim 9 where the base is selected from the group consisting of hydroxide, methoxide, ethoxide, *t*-butoxide, *t*-amylate, *s*-butoxide, di- and tribasic phosphate and carbonate.

11. A process according to claim 9 where the base is methoxide or carbonate.

12. A process according to claim 1 where the base is present in an amount of less than one equivalent.

13. A process according to claim 12 where the base is present in an amount of about 0.1 equivalents.

14. A process according to claim 1 where the catalyst is of formula (2) DuPHOS.

15. A process according to claim 1 where X_2 is BF_4^-.

16. A process according to claim 1 where X_{1-1} is $-CH_3$.

17. A process according to claim 1 where the ratio (in moles) of substrate/catalyst is from about 200/1 to 5,000/1.

18. A process according to claim 17 where the ratio (in moles) of substrate/catalyst is from about 500/1 to 3,000/1.

19. A process according to claim 18 where the ratio (in moles) of substrate/catalyst is from about 1,000/1 to 2,000/1.

20. A process according to claim 1 where the temperature at which the hydrogenation is performed is from about 20° to about 120°.

21. A process according to claim 20 where the temperature at which the hydrogenation is performed is from about 40° to about 80°.

22. A process according to claim 21 where the temperature at which the hydrogenation is performed is from about 50° to about 65°.

23. A process according to claim 1 where the pressure is from about 40 to about 1,000 psi.

24. A process according to claim 23 where the pressure is from about 70 to about 500 psi.

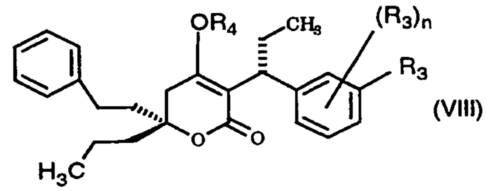
26. A process according to claim 24 where the pressure is from about 70 to about 90 psi.

26. A process according to claim 1 where the catalyst is added after the compound of formula (VII), base, solvent and hydrogen are contacted.

27. A process according to claim 26 where the catalyst is added after the compound of formula (VII), base, solvent and hydrogen are contacted and the reaction temperature is reached.

28. A process according to claim 23 where the compound (VIII) is [3α(R),6(R)]5,6-dihydro-4-hydroxy-3-[1-(3-nitrophenyl)propyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one.

29. A process for the preparation of a compound of the formula:



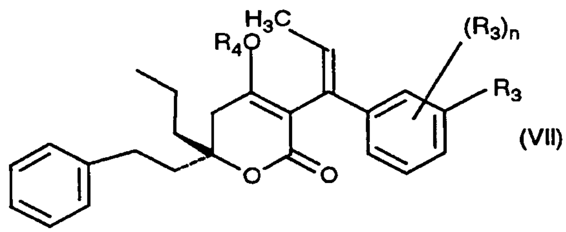
(VIII)

where R_3 is selected from the group consisting of :

- $-NO_2$,
- $-NH_2$,
- $-NH-SO_2-$[4-trifluoromethylpyridin-2-yl],
- $-N(-CH_2-\phi)_2$,
- $-N(R_{3-1})(R_{3-2})$ where R_{3-1} and R_{3-2} are the same or different and are:
  - -H,
  - -CO-O-(*t*-butyl),
  - $-CO-O-CH_2-\phi$,
  - $-CO-CH_3$,
  - $-CO-\phi$,
- -Cl,
- -Br,
- -I,
- -OH,
- $-O-SO_2-CF_3$;

where n is 0 or 1 with the provisos (1) that when n is 0 the R_3 group must be in the meta position and (2) that when n is 1, one of R_3 must be -Cl, -Br, -I, -OH or $-O-SO_2-CF_3$;

where R_4 is selected from the group consisting of Na^+, K^+, Li^+, Cs^+ and $(R_{4-1})_4N^+$ where R_{4-1} are the same or different and are CH_3-, C_2H_5-, C_4H_9-, ϕ-CH_2- and C_8H_{17}- which comprises hydrogenating a compound of the formula:



(VII)

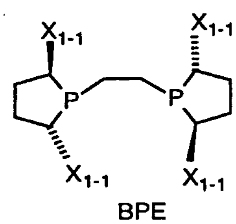
the E-geometrical isomer thereof or a mixture of the Z- and E-isomers, where R_3 and R_4 are as defined above, in the presence of catalyst containing Rh, a chiral ligand with at least one phosphorous atom.

30. A process according to claim 29 where the catalyst is the (2R,5R)-enantiomer of a catalyst of the formula:

X_1-Rh^+-cyclooctadiene X_2^-

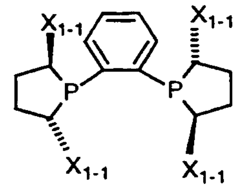
where X_1 is selected from the group consisting of:

(1) BPE



where X_{1-1} is $-CH_3$ or $-C_2H_5$,

(2) DuPHOS



DuPHOS

where X_{1-1} is as defined above;

where X_2 is selected from the group consisting of:

(1) BF_4^- and

(2) CF_3-CO-O^-.

31. A process according to claim 29 where a mixture of E/Z-isomers of (VII) is used.

32. A process according to claim 29 where n is 0.

33. A process according to claim 29 where R_3 is $-NO_2$, $-NH_2$ and $-N(R_{3-1})(R_{3-2})$ where one of R_{3-1} and R_{3-2} is -H and the other is -CO-O-(*t*-butyl).

34. A process according to claim 33 where R_3 is $-NO_2$.

35. A process according to claim 29 where R_4 is Na^+, K^+, Li^+, Cs^+ and $(R_{4-1})_4N^+$.

36. A process according to claim 29 where the catalyst is of formula (2) DuPHOS.

37. A process according to claim 29 where X_2 is BF_4^-.

38. A process according to claim 29 where X_{1-1} is $-CH_3$.

39. A process according to claim 29 where the ratio (in moles) of substrate/catalyst is from about 200/1 to 5,000/1.

40. A process according to claim 39 where the ratio (in moles) of substrate/catalyst is from about 500/1 to 3,000/1.

41. A process according to claim 40 where the ratio (in moles) of substrate/catalyst is from about 1,000/1 to 2,000/1.

42. A process according to claim 29 where the temperature at which the hydrogenation is performed is from about 20° to about 120°.

43. A process according to claim 42 where the temperature at which the hydrogenation is performed is from about 40° to about 80°.

44. A process according to claim 43 where the temperature at which the hydrogenation is performed is from about 50° to about 65°.

45. A process according to claim 29 where the pressure is from about 40 to about 1,000 psi.

46. A process according to claim 45 where the pressure is from about 70 to about 500 psi.

47. A process according to claim 46 where the pressure is from about 70 to about 90 psi.

48. A process according to claim 29 where the catalyst is added after the compound of formula (VII), base, solvent and hydrogen are contacted.

49. A process according to claim 48 where the catalyst is added after the compound of formula (VII), base, solvent and hydrogen are contacted and the reaction temperature is reached.

50. A process according to claim 29 where the compound (VIII) is [3α(R),6(R)]5,6-dihydro-4-hydroxy-3-[1-(3-nitrophenyl)propyl]-6-[1-(2-phenyl)ethyl]-6-propyl-2H-pyran-2-one.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/03720

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D309/32

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 12919 A (PHARMACIA & UPJOHN) 18 March 1999 (1999-03-18) page 30; figure XVII; example 30; tables CHART,F	1,2,29, 30
A	WO 95 30670 A (UPJOHN) 16 November 1995 (1995-11-16) claims; table CHART	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 July 2000	08/08/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/03720

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